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COMPLETE SPECIFICATION.

Medicinal Preparations for the Treatment of Prostatic Hypertrophy.

We, SCHERING AKTIENGESELLSCHAFT, a body corporate organised according to the laws of Germany, of 170—172 Mullerstrasse. Berlin N.65, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to medicinal preparations for the treatment of hypertrophic conditions of the prostrate.

It is an object of the present invention to achieve with respect to hypertrophic conditions of the prostate at least palliative relief, i.e. relief of pain, although frequently, the medicinal preparations of the invention will cause a reduction in the size of the prostate and improvement in the urinary flow.

Accordingly, this invention provides a medicinal preparation for intra-muscular injection in the treatment of hypertrophic conditions of the prostate, which comprises a solution of a 17-ester of 19-nor-17α-hydroxy-progesterone in an oily solvent.

The 17-ester present in the medicinal preparations of the invention is preferably 19 - nor - 17α - hydroxy - progesterone - 17 - caproate. Other advantageous 17-esters of 19-nor-17α-hydroxy-progesterone are the formate, acetate, butyrate, caprylate and cyclopentyl-propionate.

In the hypertrophy of the prostate, which is characterised by its long duration, within two or three months after starting the administration of a medicinal preparation of the present invention a marked improvement is observed, particularly with respect to the irritating effects which occur. Pollakisuria and nocturia are significantly reduced. Furthermore, the flow of urine is normalized and the residual volume of urine is significantly reduced or completely eliminated.

[*Price* 4*s*. 6*d*.]

Apart from the desired slow release or depot effect of, for example, 19-nor-17α-hydroxy-progesterone-17-caproate, it is a particular advantage of the preparations of the present invention that for the successful treatment of hypertrophy of the prostate a dosage of the active ingredient of from 100 to 200 mg per week will give positive results. In contrast thereto, attempts to treat hypertrophy of the prostate with other steroid compounds generally require doses of from about 2 to 3 grams per week which are administered intramuscularly in the form of oily solutions. Even assuming a high solubility of the active steroid of 250 mg per 1 ml of oil, administration of these other steroids requires the intra-muscular injection of from at least 8 to 12 ml of oil, which generally causes undesirable side effect, such as oil infiltration, hardening at the point of injection, painful reddening and inflammation or even abcesses of long duration at the points of infiltration.

A further advantage of the esters present in the preparations of the present invention, and particularly 19-nor-17α-hydroxy-progesterone caproate, is that they do not have an oestrogenic or androgenic side effect and only a slight antigonadotropic effect.

In the treatment of hypertrophy of the prostate with the preparations of this invention between 50 and 1000 mg of the 19-nor-17α-hydroxy-progesterone ester are injected intramuscularly several times per week, and th preferred treatment will be the administration of 250 mg between 2 and 3 times per week for the purpose of relieving pain, reduction of the size of prostate and improvement in the urinary flow. The administration of this medication should be continued as long as the condition of the patient requires.

The medicinal preparations of this inven-

tion are made, for example, by dissolving the 19-nor-17α-hydroxy-progesterone ester in an oily solvent, such as castor oil, by the methods known in galenic pharmacology. If desired, the solvent powder of the oily solvents can be increased by the addition of diluents or solution promoters, for example, benzyl benzoate.

The resulting solutions, which may contain, for instance, 250 mg of the active agent per millilitre, are then charged under sterile conditions into ampoules having a capacity of 1 to 2 millilitres. A preferred preparation according to the present invention is a solution of 19-nor-17α-hydroxy-progesterone-17-caproate in a mixture of 6 parts by volume of castor oil and 4 parts by volume of benzyl benzoate, the solution containing 100 mg of the caproate per millilitre of solution.

The 19 - nor - 17α - hydroxy - progesterone esters are made by the esterification of 19-nor-17α-hydroxy-progesterone with the appropriate organic carboxylic acids by methods in themselves known, for example, by the esterification of 19-nor-17α-hydroxy-progesterone with caproic acid/caproic anhydride and saponification of the 3-enol-ester group, intermediately formed, in acid solution or, in aqueous sodium hydroxide solution. The isolated 19-nor-17α-hydroxy-progesterone caproate, after recrystallization from isopropyl ether, melts at 123—124°C.

The following Examples illustrate methods of making certain of the 17-esters of 19-nor-17α-hydroxy-progesterone to be incorporated in the medicinal preparations of the invention:

Example 1

300 mg of 19-nor-17α-hydroxy-progesterone are dissolved in a mixture of 17 cc of acetic anhydride and 42 cc of 95% formic acid which has been standing for 6 hours at 0°C. 345 mg of p-toluene sulphonic acid $\cdot 1\,H_2O$ are added under ice cooling and nitrogen atmosphere. The reaction mixture is allowed to stand for 16 hours at room temperature. The clear solution is poured into a mixture of pyridine in ice water and filtered under suction after 1 hour to obtain the crude 17α-hydroxy-norprogesterone-formate as a precipitate. The precipitate is dried and recrystallized from isopropyl ether. There is thus obtained a yield of 265 mg of pure 19-nor-17α-hydroxy-progesterone-17-formate melting at 198—199.5°C.

U.V. $\epsilon_{239}=17{,}000$.

Example 2

380 mg of p-toluene sulphonic acid $\cdot 1\,H_2O$ are added to a suspension of 316 mg of 19-nor-17α-hydroxy-progesterone in 16 cc of acetic anyhydride. The esterification is completed after 4 hours at 37°C. The excess of acetic anhydride is decomposed with pyridine in ice water and the 3-enol-17-diester is extracted with ether. The ethereal extract is washed until neutral, dried over sodium sulphate and concentrated. The residue was dissolved in 35 cc of methanol, reacted with 0.35 cc of concentrated hydrochloric acid and heated under refluxing for 1 hour. The methanolic solution is diluted with water and extracted with ether. The ethereal extract is washed with water until neutral and dried over sodium sulphate and then concentrated. The substance is recrystallized from isopropyl ether for purification. There is thus obtained a yield of 250 mg of pure 19-nor-17α-hydroxy-progesterone-17-acetate melting at 214—216°C.

U.V. $\epsilon_{239}=17{,}000$.

Example 3

1.32 grams of p-toluene sulphonic acid $\cdot 1\,H_2O$ are added to a solution of 1.0 gram of 19-nor-17α-hydroxy-progesterone in 32 cc of caproic anhydride under stirring and under a nitrogen atmosphere. After 3 hours at 37°C. the reaction is completed. The clear light-yellow solution is taken up in a mixture of 1.43 cc of concentrated hydrochloric acid in 143 cc of methanol, and heated under refluxing and under nitrogen for 1 hour. The excess of caproic acid is removed by steam distillation and the residue is extracted with ether. The ethereal extract is washed with water until neutral, dried over sodium sulphate and concentrated. The precipitated crude product is recrystallized from isopropyl ether.

The yield amounts to 1.1 grams of pure 19 - nor - 17α - hydroxy - progesterone - 17 - caproate melting at 123—124°C.

U.V. $\epsilon_{239}=17{,}540$.

Example 4

0.66 gram of p-toluene sulphonic acid $\cdot 1\,H_2O$ are added to a suspension of 0.5 gram of 19-nor-17α-hydroxy-progesterone in 20 cc of butyric anhydride under stirring and under a nitrogen atmosphere. After 4 hours at 37°C, 70 cc of methanol and 0.7 cc of concentrated hydrochloric acid are added to the clear solution, and the whole is cooked for 1 hour under refluxing and under a nitrogen atmosphere. The reaction mixture is extracted with ether, the ethereal extract is washed until neutral, dried over sodium sulphate and concentrated.

Recrystallization from isopropyl ether results in pure 19-nor-17α-hydroxy-progesterone-17-butyrate.

U.V. $\epsilon_{239}=17{,}200$.

Example 5

920 mg of p-toluene sulphonic acid $\cdot 1\,H_2O$ are added to a suspension of 0.7 gram of 19-nor-17α-hydroxy-progesterone in 30 cc of caprylic anhydride under a nitrogen atmosphere. After 3 hours of stirring at 37°C the solution is diluted with 100 cc of methanol, and after the addition of 1 cc of concentrated hydrochloric acid, the whole is heated for 1 hour under refluxing. The excess of caprylic acid is removed by steam distillation. The residue is taken up in ether, the ethereal extract is washed until neutral, dried over sodium sulphate and concentrated.

The thus obtained oil is dissolved in isopropyl ether, purified with activated carbon and the thus obtained colourless solution is again concentrated to dryness. The resulting oily residue is found upon elemental analysis and upon tests under ultra-violet and infra-red light to be pure 19-nor-17α-hydroxy-progesterone-17-caprylate.

U.V. $\epsilon_{239}=17{,}100$.

Example 6

1 gram of 19-nor-17α-hydroxy-progesterone is added to a mixture heated to a temperature of 80°C of 4 cc of cyclopentyl-propionic acid and 1 cc of trifluoroacetic anhydride. After 35 minutes of reaction at the same temperature the clear solution is added to water, the precipitated oil is taken up in ether, the ethereal extract is first washed with a saturated sodium carbonate solution, and subsequently with water until neutral. It is then dried over sodium sulphate and concentrated. The resulting crude oil is dissolved in isopropyl ether, purified with activated carbon, and the resulting colourless solution is concentrated to dryness. The colourless oily residue can definitely be identified as 19-nor-17α-hydroxy-progesterone-17-cyclopentylpropionate.

U.V. $\epsilon_{239}=17{,}400$.

A medicinal preparation of the present invention may be prepared, for example, from 25 mg of 19-nor-17α-hydroxy-progesterone-17-caproate by dissolving the latter in 0.6 ml of castor oil and 0.4 ml of benzyl benzoate, or by dissolving the above caproate or other ester of 19-nor-17α-hydroxy-progesterone in 1.0 ml of sesame oil. The oily solution is then passed through a sterile filter. Ampoules are filled with the solution under aseptic conditions. After the ampoules have been sealed they are sterilised by heating for one hour at 120°C.

Generally it is desirable to use for intramuscular administration for the treatment hypertrophy of the prostate, oily solutions containing between 50 and 250 mg of the 19-nor-17α-hydroxy-progesterone ester per millilitre.

WHAT WE CLAIM IS:—

1. A medicinal preparation for intramuscular injection in the treatment of hypertrophic conditions of the prostate, which comprises a solution of 17-ester of 19-nor-17α-hydroxy-progesterone in an oily solvent.
2. A medicinal preparation as claimed in claim 1, wherein the solution also contains a solution promoter.
3. A medicinal preparation as claimed in claim 2, wherein the solution promoter is benzyl benzoate.
4. A medicinal preparation as claimed in any one of claims 1 to 3, wherein the solvent comprises castor oil.
5. A medicinal preparation as claimed in claim 4, wherein the solvent is a mixture of 6 parts by volume of castor oil and 4 parts by volume of benzyl benzoate.
6. A medicinal preparation as claimed in any one of claims 1 to 5, which contains about 100 milligrams of the 17-ester per millilitre of the solution.
7. A medicinal preparation as claimed in any one of claims 1 to 6, wherein the said ester is a 19-nor-17α-hydroxy-progesterone-17-caproate.
8. A medicinal preparation as claimed in any one of claims 1 to 6, wherein the said ester is the 17-formate, 17-acetate, 17-butyrate, 17-caprylate or 17-cyclopentyl-propionate of 19-nor-17-α-hydroxy-progesterone.
9. A medicinal preparation as claimed in any one of claims 1 to 8, which contains from 50 to 250 milligrams of the 17-ester per millilitre of the solution.

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